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(51) International Patent Classification ⁷ : C07D 498/04, A61K 31/5383, A61P 35/00, 5/32, C07D 498/04 // (C07D 311/00, 265:00)		A2	(11) International Publication Number: WO 00/66590 (43) International Publication Date: 9 November 2000 (09.11.00)
(21) International Application Number: PCT/US00/11750 (22) International Filing Date: 1 May 2000 (01.05.00) (30) Priority Data: 09/304,614 4 May 1999 (04.05.99) US 09/552,353 19 April 2000 (19.04.00) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/552,353 (CON) Filed on 19 April 2000 (19.04.00) (71) Applicants (for all designated States except US): LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US). AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07840 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ZHI, Lin [CN/US]; 7794 Roan Road, San Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). MARSCHKE, Keith, B. [US/US]; 12565 Escala		Drive, San Diego, CA 92128 (US). TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). FENSOME, Andrew [GB/US]; 779 Trephanny Lane, Wayne, PA 19087 (US). ZHANG, Puwen [CN/US]; 7004 Oriole Court, Audubon, PA 19403 (US). (74) Agents: KODROFF, Cathy, A. et al.; Howson & Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: TETRACYCLIC PROGESTERONE RECEPTOR MODULATOR COMPOUNDS AND METHODS			
(57) Abstract <p>Nonsteroidal compounds that are high affinity, high selectivity modulators for progesterone receptors are disclosed. Also disclosed are pharmaceutical compositions incorporating such compounds, methods for employing the disclosed compounds and compositions for treating patients requiring progesterone receptor agonist, partial agonist or antagonist therapy, intermediates useful in the preparation of the compounds and processes for the preparation of the progesterone receptor modulator compounds.</p>			

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TETRACYCLIC PROGESTERONE RECEPTOR MODULATOR COMPOUNDS
AND METHODS

Field of the Invention

5 This invention relates to nonsteroidal tetracyclic compounds that are modulators (i.e. agonists and antagonists) of progesterone receptors, and to methods for the making and use of such compounds.

Background of the Invention

10 Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroidal PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins, such as norgestrel, as female birth control agents must be weighed
15 against the increased risk of breast cancer and heart disease to women taking such agents. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could cause homeostatic imbalances in a patient due to its inherent cross-reactivity as a glucocorticoid receptor (GR) antagonist. Accordingly, identification of compounds that
20 have good specificity for PR, but have reduced or no cross-reactivity for other steroid receptors, would be of significant value in the improvement of women's health.

 Nonsteroidal molecules that contain a di- or tetrahydroquinoline ring as the core pharmacophore have been described as steroid receptor modulator compounds. {See for example: "Preparation of Quinolines and Fused Quinolines as Steroid Receptor
25 Modulators", T. K. Jones, M. E. Goldman, C. L. F. Pooley, D. T. Winn, J. P. Edwards, S. J. West, C. M. Tegley, L. Zhi, L. G. Hamann, R. L. Davis, L. J. Farmer, PCT Int. Appl. Pub. No. WO 96/19458; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, D. T. Winn, L. Zhi, L. G. Hamann, C. M. Tegley, C. L. F. Pooley, US Patent No. 5,688,808; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, M. E. Goldman, C. L.
30 F. Pooley, D. T. Winn, J. P. Edwards, S. J. West, C. M. Tegley, L. Zhi, US Patent No.

- 5,688,810; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, C. M. Tegley, L. Zhi, J. P. Edwards, S. J. West, US Patent No. 5,693,646; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, L. Zhi, C. M. Tegley, D. T. Winn, L. G. Hamann, J. P. Edwards, S. J. West, US Patent No. 5,693,647; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, L. Zhi, J. P. Edwards, C. M. Tegley, S. J. West, US Patent No. 5,696,127; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, D. T. Winn, M. E. Goldman, L. G. Hamann, L. Zhi, L. J. Farmer, R. L. Davis, US Patent No. 5,696,130; "Steroid Receptor Modulator Compounds and Methods", T. K. Jones, M. E. Goldman, C. L. F. Pooley, D. T. Winn, J. P. Edwards, S. J. West, C. M. Tegley, L. Zhi, L. G. Hamann, L. J. Farmer, R. L. Davis, US Patent No. 5,696,133.}
- Molecules containing a bicyclic heterocycle have been reported as cardiotonic agents. {See: "A Novel Class of Cardiotonic Agents: Synthesis and Biological Evaluation of 5-Substituted 3,6-Dihydrothiadiazin-2-ones with Cyclic AMP Phosphodiesterase Inhibiting and Myofibrillar Calcium Sensitizing Properties", M.-C. Forest, P. Lahouratate, M. Martin, G. Nadler, M. J. Quiniou, R. G. Zimmermann, *J. Med. Chem.* 35 (1992) 163-172; "Heteroatom Analogues of Bemoradan: Chemistry and Cardiotonic Activity of 1,4-Benzothiazinylpyridazinones", D. W. Combs, M. S. Rampulla, J. P. Demers, R. Falotico, J. B. Moore, *J. Med. Chem.*, 35 (1992) 172-176. }

20

Summary of the Invention

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by PR. More particularly, the invention relates to nonsteroidal compounds and compositions that are high affinity, high specificity agonists, partial agonists (i.e., partial activators and/or tissue-specific activators) and antagonists for progesterone receptors. Also provided are methods of making such compounds and pharmaceutical compositions, as well as critical intermediates used in their synthesis.

25

These and various other advantages and features of novelty that characterize the invention are pointed out with particularity in the claims annexed hereto and forming a part hereof. However, for a better understanding of the invention, its advantages, and objects

obtained by its use, reference should be had to the accompanying descriptive matter, in which preferred embodiments of the invention are described.

5

Detailed Description of the Invention

As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The terms alkyl, alkenyl, alkynyl and allyl include optionally substituted straight-chain, branched-chain, cyclic, saturated and/or unsaturated structures, and combinations thereof.

The term haloalkyl refers to alkyl structures, including straight-chain, branched-chain, or cyclic structures, or combinations thereof, that are substituted with one or more fluorines, chlorines, bromines or iodines, or combinations thereof.

The term heteroalkyl includes straight-chain, branched-chain, cyclic, saturated and/or unsaturated structures, or combinations thereof, in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

The term aryl refers to an optionally substituted six-membered aromatic ring.

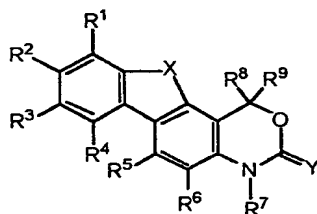
The term heteroaryl refers to an optionally substituted, aromatic five-membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, or to an optionally substituted, aromatic six-membered heterocyclic ring containing one or more nitrogens.

The substituents of an "optionally substituted" structure include, but are not limited to, one or more of the following preferred substituents: F, Cl, Br, I, CN, NO₂, NH₂, NCH₃, OH, OCH₃, OCF₃, CH₃, CF₃.

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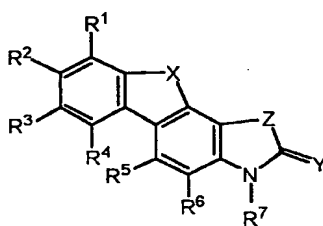
Compounds of the present invention are defined as those having the formula:

-4-



(I)

OR



(II)

5

wherein:

- R^1 through R^6 are independently hydrogen, F, Cl, Br, I, NO_2 , CN, OR^{10} , $\text{NR}^{10}\text{R}^{11}$, SR^{10} , COR^{12} , CO_2R^{12} , $\text{CONR}^{10}\text{R}^{11}$, optionally substituted C_1 to C_6 alkyl or heteroalkyl, C_1 to C_6 haloalkyl, optionally substituted C_3 to C_8 cycloalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted aryl or heteroaryl, or optionally substituted arylmethyl, where R^{10} and R^{11} are independently hydrogen, C_1 to C_6 alkyl or heteroalkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl, optionally substituted arylmethyl, COR^{13} , SO_2R^{13} or S(O)R^{13} , where R^{12} is hydrogen, C_1 to C_6 alkyl or heteroalkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl or optionally substituted arylmethyl, where R^{13} is hydrogen, C_1 to C_6 alkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl or optionally substituted arylmethyl;
- 10
- 15

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R^7 is hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, aryl, arylmethyl, heteroaryl, COR^{12} , CO_2R^{12} , SO_2R^{12} , $S(O)R^{12}$ or $CONR^{10}R^{11}$, where R^{10-12} have the same definitions given above;

R^8 and R^9 are independently hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted arylmethyl, optionally substituted aryl or optionally substituted heteroaryl;

X is OCH_2 , SCH_2 , $NHCH_2$, $OC(O)$, $SC(O)$, $NHC(O)$, CH_2O , CH_2S , CH_2NH , $C(O)O$, $C(O)S$ or $C(O)NH$;

Y is O, S or NR^{10} , where R^{10} has the same definition given above; and

10 Z is O, S, NR^{14} , $CR^{14}R^{15}$, $CR^{14}R^{15}CR^{16}R^{17}$, $OCR^{14}R^{15}$, $SCR^{14}R^{15}$, $CR^{14}R^{15}S$, $NR^{14}CR^{15}R^{16}$, or $CR^{14}R^{15}NR^{16}$, where R^{14} through R^{17} each independently are hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted arylmethyl, optionally substituted aryl or optionally substituted heteroaryl;

15 or a pharmaceutically acceptable salt thereof.

In a preferred aspect, the present invention provides a pharmaceutical composition comprising an effective amount of an progesterone receptor modulating compound of formula I or formula II shown above wherein R^{1-17} , X, Y and Z all have the same definitions as given above.

20 In a further preferred aspect, the present invention comprises a method of modulating processes mediated by progesterone receptors comprising administering to a patient an effective amount of a compound of formula I or formula II shown above, wherein R^{1-17} , X, Y and Z all have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as
25 pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic,

nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional

5 pharmaceutically acceptable salts are known to those skilled in the art.

The PR agonist, partial agonist and antagonist compounds of the present invention are particularly useful for female hormone replacement therapy and as modulators of fertility (e.g., as contraceptives or contragestational agents), either alone or in conjunction with estrogen receptor modulators. The PR modulator compounds are also used in the treatment
10 of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flashes, mood disorders, meningiomas as well as in various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as a selective agonists, partial agonists or
15 antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (e.g., progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare-ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be
20 useful to control water balance in the body, while the AR effects would help to control any acne flare-ups that occur.

Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the
25 conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

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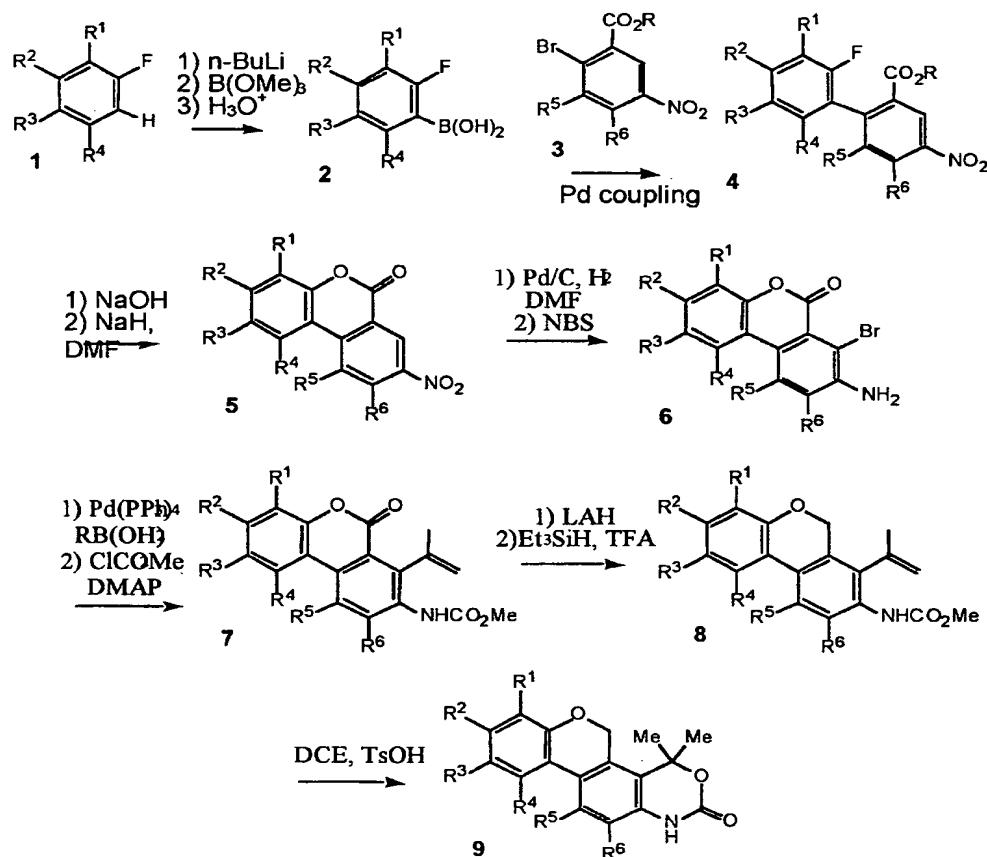
Representative PR modulator compounds (i.e., agonists, partial agonists and antagonists) according to the present invention include: 7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 14); 9-bromo-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 20); 7-fluoro-9-formyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 24); 7-fluoro-9-hydroxyiminomethyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 25); 9-cyano-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 26).

Compounds of the present invention, comprising classes of heterocyclic nitrogen compounds and their derivatives, can be obtained by routine chemical synthesis by those skilled in the art, for example, by modification of the heterocyclic nitrogen compounds disclosed or by a total synthesis approach.

The sequences of steps to synthesize the compounds of the present invention are shown below in the general schemes. In each of the Schemes the R groups (e.g., R¹, R², etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulas I and II also comprise potential substituents for the analogous positions on the structures within the Schemes. In a further aspect, the present invention provides a novel process for the preparation of the compounds of the present invention.

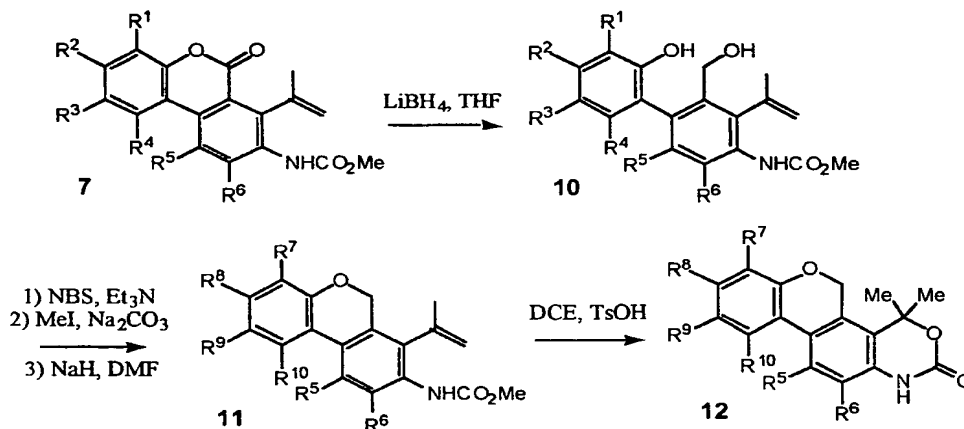
Scheme I

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The process of **Scheme I** begins with the preparation of fluoroboronic acid **2** by a literature procedure, in which ortho-lithiation of fluorobenzene **1** with an alkyl lithium reagent, such as *n*-butyllithium (*n*-BuLi) or *tert*-butyllithium, in THF or ether at -78 to -50 °C followed by addition of a trialkyl borate, such as trimethyl or triisopropyl borate, at -78 °C and acidification with an aqueous acid, such as HCl, provides boronic acid **2**. Biaryl compound **4** is prepared by a typical palladium catalyzed coupling reaction of boronic acid **2** and bromobenzoate **3** under aqueous or nonaqueous conditions at ambient temperature. The ester **4** is hydrolyzed under basic conditions, such as THF/MeOH/2N Na_2CO_3 , at ambient

temperature, and the resulting carboxylate is heated at elevated temperature in a polar solvent, such as DMF, to generate lactone 5. The nitro-lactone 5 is converted to aminobromo-lactone 6 in a one-pot two-step procedure that involves reduction of the nitro group to an amino group under hydrogen atmosphere (catalyzed by palladium on carbon) followed by bromination with N-bromosuccinimide (NBS) in DMF at room temperature. The isopropenyl group is introduced by a palladium-catalyzed coupling reaction, for example, Suzuki coupling reaction between isopropenylboronic acid and bromo compound 6. The resulting amino compound is then converted to the carbamate 7 by treatment with methyl chloroformate in the presence of 4-dimethylaminopyridine. Removal of the carbonyl group of lactone 7 is completed by stepwise reduction with typical reducing agents such as LiAlH_4 and Et_3SiH in the presence of a catalytic amount of acid (e.g., TFA) to afford compound 8. The final product 9 is obtained by the treatment of compound 8 with tosic acid (TsOH , *p*-toluenesulfonic acid) in refluxing dichloroethane (DCE).

Scheme II

Scheme II describes a four-step, selective D-ring modification procedure, in which reduction of lactone 7 with a reducing agent such as LiBH_4 provides diol 10 and then NBS bromination of diol 10 in the presence of a base such as triethylamine followed by a selective methylation and NaH mediated nucleophilic cyclization in DMF affords compound 11.

-10-

Treatment of compound **11** with more than one equivalent of an acid such as TsOH in refluxing dichloroethane provides compound **12**.

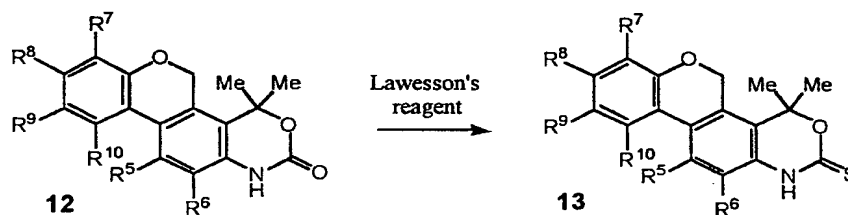
Scheme III involves selective D-ring functional group conversion from R^{1-4} to R^{7-10} by known substituent group conversions such as converting bromo to aldehyde by metal-halogen exchange followed by nucleophilic addition to DMF, or converting an aldehyde to an oxime by hydroxylamine treatment of the aldehyde, or converting an oxime to a cyano group by treatment of the oxime with thionyl chloride.

Scheme III



10

Scheme IV



Scheme IV describes the conversion of compound **12** to its cyclic thiocarbamate analogue **13** by Lawesson's reagent (p-methoxyphenylthionophosphine sulfide dimer).

It will be understood by those skilled in the art that certain modifications can be made to the above-described methods that remain within the scope of the present invention.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds.

Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, e.g., intravenous, oral, topical, suppository or parenteral.

In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions such as Eucerin™ (Beiersdorf). Examples of suitable cream bases are Nivea™ Cream (Beiersdorf), cold cream (USP), Purpose Cream™ (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm™ (Warner-Lambert).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (e.g., tablet, capsule etc.) at from about 1 µg/kg of body weight to about 500 mg/kg of body weight, more preferably from

about 10 µg/kg to about 250 mg/kg, and most preferably from about 20 µg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition
5 of the patient, and tolerance for the drug.

The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. They are particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of
10 other steroid receptors or related intracellular receptors.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors
15 of choice, and then separating out the bound ligand/receptor combination by separation techniques that are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

The compounds and pharmaceutical compositions of the present invention possess a
20 number of advantages over previously identified steroid modulator compounds. For example, the compounds are extremely potent activators of PR, preferably displaying 50% maximal activation of PR at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM or less. Also, the selective compounds of the present invention generally do not display
25 undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR, thereby limiting its use in long-term, chronic administration. In addition, the compounds of the present invention, as small organic molecules, are easier to

synthesize, provide greater stability and can be more easily administered in oral dosage forms than other known steroidal compounds.

The invention will be further illustrated by reference to the following non-limiting Examples.

5

EXAMPLE 1

7-Fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 14; Structure 9 of Scheme I, where R¹ = fluoro, R²⁻⁶ = H)

10 2,3-Difluoroboronic acid (Structure 2 of Scheme I, where R¹ = fluoro, R²⁻⁴ = H)

To a 500 mL flask charged with a solution of 1,2-difluorobenzene (15 g, 0.13 mmol) in THF (150 mL) at -78 °C was added dropwise *n*-BuLi (7.0 M in hexane, 19 mL, 0.13 mol). The reaction mixture was stirred at -78 °C for 2.5 hours and then a solution of trimethylborate (30 mL, 0.26 mol, 2.0 equiv) in THF (90 mL) previously cooled to -78 °C was added, after which the mixture was allowed to warm up to room temperature overnight. Next the reaction mixture was acidified to pH ~ 1 using HCl (3 N aqueous) and then stirred for 15 minutes. Then the mixture was extracted with ether (2 × 300 mL), washed with water (150 mL) and dried over Na₂SO₄. The solvent was removed *in vacuo* to yield 20 g (96%) of 2,3-difluoroboronic acid as a white solid. Data for 2,3-difluoroboronic acid: rf = 0.39 (EtOAc:hexanes, 3:7).

20

Methyl 2-(2,3-Difluorophenyl)-5-nitrobenzoate (Compound 15; Structure 4 of Scheme I, where R¹ = fluoro, R²⁻⁶ = H)

A mixture of 2,3-difluoroboronic acid (20g, 0.12 mol, 1.3 equiv), methyl 2-bromo-5-nitrobenzoate (25 g, 96 mmol) (Structure 3, where R = methyl, R⁵⁻⁶ = H), tetrakis(triphenylphosphine)palladium(0) (3.6 g, 3.1 mmol, 3.2% equiv) and aqueous sodium carbonate (2 M, 200 mL) in toluene (200 mL) and ethanol (100 mL) was heated at reflux overnight until completion of the reaction was indicated by TLC. The reaction mixture was extracted with EtOAc (2 × 400 mL), washed with brine (300 mL) and dried over Na₂SO₄.

25

Removal of solvent provided a brown solid, which was recrystallized from *i*-PrOH:hexanes to give Compound 15 (22.8 g, 83%) as a white solid. Data for 15: $r_f = 0.32$ (CH_2Cl_2 :hexanes, 4:6); ^1H NMR (400 MHz, CDCl_3) δ 8.87 (d, $J = 1.2$, 1 H), 8.43 (dd, $J = 8.3$ and 1.2 , 1 H), 7.58 (d, $J = 8.6$, 1 H), 7.29-7.17 (m, 2 H), 7.10-7.02 (m, 1 H) and 3.82 (s, 3 H).

4-Fluoro-8-nitro-6H-dibenzo[*b,d*]pyran-6-one (Compound 16; Structure 5 of Scheme I, where $\text{R}^1 = \text{fluoro}$, $\text{R}^{2-6} = \text{H}$)

To a solution of Compound 15 (20 g, 69 mmol) in THF:MeOH (~2.5:1) (370 mL) was added 10% aqueous NaOH (82 mL), and the reaction mixture was stirred at room temperature for 1 hour. The mixture was concentrated, acidified to pH ~ 1 using 3N HCl and then extracted with EtOAc (2 \times 400 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford the acid as an off-white solid. To a solution of the crude acid in dry DMF (180 mL) was added NaH (4.0 g, 1.5 equiv), and the mixture was heated at ~80 °C for 2 hours, at which time TLC indicated completion of the reaction. The reaction mixture was concentrated under reduced pressure to a small volume, and then water (5 mL) was added. The mixture was cooled to -15 °C to afford a white precipitate, which was filtered and washed with cold water and hexane to give Compound 16 (17 g, 95%). Data for 16: $r_f = 0.36$ (EtOAc:hexanes, 3:7); ^1H NMR (400 MHz, CDCl_3) δ 9.28 (d, $J = 1.1$, 1 H), 8.68 (dd, $J = 8.5$ and 1.1 , 1 H), 8.32 (d, $J = 8.5$, 1 H), 7.91 (d, $J = 8.0$, 1 H) and 7.46-7.36 (m, 2 H).

8-Amino-7-bromo-4-fluoro-6H-dibenzo[*b,d*]pyran-6-one (Compound 17; Structure 6 of Scheme I, where $\text{R}^1 = \text{fluoro}$, $\text{R}^{2-6} = \text{H}$)

A mixture of Compound 16 (8.8 g, 34 mmol) and 10% Pd/C (0.95 g, 2.5% equiv.) in DMF (150 mL) in a Parr apparatus was shaken at room temperature under H_2 (40-60 psi) overnight until completion of the hydrogenation was indicated by TLC. The reaction mixture was then carefully passed through filter paper to remove all traces of Pd/C catalyst. NBS (6.0 g, 34 mmol) was added to the filtrate, and the resulting mixture was stirred at

room temperature for 2-3 hours. The mixture was concentrated under reduced pressure, and then water was added to initiate precipitation. The solid was filtered and washed with cold water to afford Compound 17 (8.6 g, 83%) as a pale brown solid. Data for 17: $r_f = 0.11$ (EtOAc:hexanes, 1:3); $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.20 (d, $J = 8.8$, 1 H), 7.97 (d, $J =$
5 8.0, 1 H), 7.38 (d, $J = 8.8$, 1 H), 7.35-7.27 (m, 2 H), 6.24 (s, 2 H).

4-Fluoro-7-isopropenyl-8-methoxycarbonylamino-6H-dibenzo[*b,d*]pyran-6-one (Compound 18: Structure 7 of Scheme I, where $R^1 = \text{fluoro}$, $R^{2-6} = \text{H}$)

To a solution of 2-bromopropene (1.2 g, 10 mmol) in THF (25 mL) at -78°C was
10 added *t*-BuLi (1.7 M in pentane, 12 mL, 20 mmol), and the resulting yellow solution was stirred for 10 minutes. Trimethylborate (3.0 mL, 26 mmol) was added via syringe, and the reaction mixture was warmed up slowly overnight to yield a white slurry. The reaction mixture was acidified to pH ~ 2 , stirred at room temperature for 1 hour, extracted with EtOAc (2×50 mL), washed with brine and then was concentrated to afford the crude
15 boronic acid as a white solid.

A mixture of this crude boronic acid, Compound 17 (1.5 g, 4.8 mmol), K_2CO_3 (2.8 g, 20 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.10 g, 0.087 mmol, 1.8% equiv) in toluene (45 mL), EtOH (45 mL) and water (20 mL) was heated at reflux for 2 hours. The dark reaction mixture was acidified to pH ~ 2 and extracted with EtOAc (2×150 mL). Removal of solvent provided a
20 crude dark solid that contained 8-amino-4-fluoro-7-isopropenyl-6H-dibenzo[*b,d*]pyran-6-one. To the crude mixture in THF (40 mL) at room temperature was added ClCO_2Me (1.7 mL, 20 mmol) and DMAP (0.53 g, 4.3 mmol), and the resulting cloudy solution was stirred at room temperature for 5 hours. The reaction was quenched with water (50 mL), and the reaction mixture was extracted with EtOAc and washed with aqueous Na_2CO_3 , NH_4Cl and
25 brine. Removal of solvent and chromatography of the crude mixture afforded Compound 18 (0.35 g, 26%) as a pale yellow solid. Data for 18: $r_f = 0.34$ (EtOAc:Hexane, 1:3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.72 (d, $J = 8.9$, 1 H), 8.08 (d, $J = 9.0$, 1 H), 7.79 (bd, $J = 6.5$, 1 H), 7.54 (s, 1 H), 7.24-7.18 (m, 2 H), 5.52 (s, 1 H), 4.95 (s, 1 H), 3.81 (s, 3 H) and 2.14 (s, 3 H).

4-Fluoro-7-isopropenyl-8-methoxycarbonylamino-6H-dibenzo[b,d]pyran (Compound 19; Structure 8 of Scheme I, where R¹ = fluoro, R²⁻⁶ = H)

To a solution of Compound 18 (70 mg, 0.21 mmol) in THF (8 mL) was added
5 LiAlH₄ (8.0 mg, 0.21 mmol), and the resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with water, and the reaction mixture was extracted with EtOAc and concentrated. Chromatography afforded 4-fluoro-6-hydroxy-7-isopropenyl-8-methoxycarbonylamino-6H-dibenzo[b,d]pyran (20 mg, 28%) as a yellow solid, which was treated with a catalytic amount of TFA in the presence of Et₃SiH (0.2 mL) and CH₂Cl₂ (4
10 mL) for 2 hours at room temperature. Purification provided Compound 19 (13 mg, 68%) as a solid. Data for 19: ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 8.2, 1 H), 7.61 (d, *J* = 8.6, 1 H), 7.46 (d, *J* = 7.5, 1 H), 7.04-6.93 (m, 2 H), 6.89 (s, 1 H), 5.55 (s, 1 H), 5.10 (d, *J* = 13.5, 1 H), 5.07 (d, *J* = 13.5, 1 H), 5.03 (s, 1 H), 3.79 (s, 3 H) and 2.01 (s, 3 H).

15 7-Fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 14; Structure 9 of Scheme I, where R¹ = fluoro, R²⁻⁶ = H)

A mixture of Compound 19 (13 mg, 0.041 mmol) and TsOH (16 mg, 0.084 mmol) in dichloroethane (5 mL) was heated at reflux for 15 hours and concentrated. The mixture was diluted in EtOAc (20 mL) and was washed with aqueous Na₂CO₃ (2 × 5 mL) and brine.
20 Removal of solvent provided the product as a white solid, which was recrystallized from EtOAc:hexanes to yield 6 mg (49%) of Compound 14 as a white solid. Data for 14: ¹H NMR (400 MHz, CDCl₃) δ 8.71 (bs, 1 H), 7.58 (d, *J* = 8.4, 1 H), 7.40 (d, *J* = 7.4, 1 H), 7.08-6.95 (m, 2 H), 6.88 (d, *J* = 8.4, 1 H), 5.24 (s, 2 H) and 1.84 (s, 6 H).

EXAMPLE 2

9-Bromo-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one
(Compound 20; Structure 12 of Scheme II, where R⁷ = fluoro, R⁹ = bromo,
R⁵⁻⁶ = R⁸ = R¹⁰ = H)

5

N-Methoxycarbonyl-3-hydroxymethyl-4-(3-fluoro-2-hydroxyphenyl)-2-isopropenylaniline
(Compound 21; Structure 10 of Scheme II, where R¹ = fluoro, R²⁻⁶ = H)

To a solution of Compound 18 (Structure 7 of Scheme II, where R¹ = fluoro, R²⁻⁶ = H) (0.33 g, 1.0 mmol) in THF (30 mL) was added LiAlH₄ (44 mg, 2.0 mmol) portionwise at
10 room temperature, and the resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, and the reaction mixture was extracted with EtOAc. Removal of solvent followed by chromatography afforded Compound 21 (0.30 g, 96%) as a colorless oil. Data for 21: rf = 0.11 (EtOAc:hexanes, 1:3); ¹H NMR (400 MHz, CDCl₃) showed a mixture of rotomers.

15

N-Methoxycarbonyl-3-hydroxymethyl-4-(5-bromo-3-fluoro-2-hydroxyphenyl)-2-isopropenylaniline
(Compound 22; Structure 10 of Scheme II, where R¹ = fluoro, R³ = bromo, R² = R⁴⁻⁶ = H)

NBS (0.18 g, 1.0 mmol) was added to a mixture of Compound 21 (0.30 g, 0.96
20 mmol) and Et₃N (1.0 mL) in CH₂Cl₂ (12 mL) at room temperature. After 10 minutes, the mixture was diluted with EtOAc (50 mL), and washed with water, aqueous NH₄Cl and brine. Removal of solvent and chromatography of the residue provided 0.34 g (86%) of Compound 22 as a yellow oil. Data for 22: rf = 0.12 (EtOAc:hexanes, 1:3).

25

2-Bromo-4-fluoro-7-isopropenyl-8-methoxycarbonylamino-6H-dibenzo[b,d]pyran
(Compound 23; Structure 11 of Scheme II, where R⁷ = fluoro, R⁹ = bromo, R⁵⁻⁶ = R⁸ = R¹⁰ = H)

To a solution of Compound 22 (0.34 g, 0.83 mmol) in DMF (10 mL) was added K₂CO₃ (0.14 g, 1.0 mmol) and MeI (0.5 mL, excess), and the mixture was stirred at room

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temperature for 1 hour. Standard work-up followed by chromatography afforded 0.28 g (78%) of N-methoxycarbonyl-2-isopropenyl-3-hydroxymethyl-4-(5-bromo-3-fluoro-2-methoxyphenyl)aniline. Data for the methylated intermediate: $r_f = 0.52$ (EtOAc:hexanes, 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3) (rotomers) δ 8.13/8.02 (bs, 1 H), 7.30 (m, 1 H), 7.17-6.95 (m, 3 H), 5.61/5.53 (s, 1 H), 5.21/4.97 (s, 1 H), 4.50-4.12 (m, 2 H), 3.79/2.95 (s, 3 H), 3.62/2.88 (s, 3 H) and 2.20/2.02 (s, 3 H).

A mixture of the methylated intermediate (0.28 g, 0.65 mmol) and NaH (30 mg, 0.75 mmol) in DMF (10 mL) was heated in an 80 °C oil bath for 2 hours until the reaction went to completion. Standard work-up followed by chromatography afforded 0.20 g (80%) of Compound **23** as a solid. Data for **23**: $r_f = 0.65$ (EtOAc:hexanes, 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.15 (d, $J = 8.7$, 1 H), 7.58 (m, 1 H), 7.56 (d, $J = 8.7$, 1 H), 7.15 (dd, $J = 9.5$ and 2.0, 1 H), 6.89 (s, 1 H), 5.56 (s, 1 H), 5.09 (d, $J = 12$, 1 H), 5.07 (d, $J = 12$, 1 H), 5.03 (s, 1 H), 3.79 (s, 3 H) and 2.00 (s, 3 H).

9-Bromo-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound **20**; Structure **12** of Scheme II, where $\text{R}^7 = \text{fluoro}$, $\text{R}^9 = \text{bromo}$, $\text{R}^{5-6} = \text{R}^8 = \text{R}^{10} = \text{H}$)

A mixture of Compound **23** (0.12 g, 0.31 mmol) and TsOH (0.12 g, 0.62 mmol) in dichloroethane (15 mL) was heated at reflux for 15 hours and concentrated. The mixture was diluted in EtOAc (50 mL) and then washed with aqueous Na_2CO_3 (2×10 mL) and brine. Removal of solvent provided the product as a white solid, which was recrystallized from EtOAc:hexanes to give 60 mg (49%) of Compound **20**. Data for **20**: $r_f = 0.30$ (EtOAc:hexanes, 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.09 (s, 1 H), 7.53 (d, $J = 8.3$, 1 H), 7.52 (m, 1 H), 7.19 (dd, $J = 9.4$ and 1.9, 1 H), 5.22 (s, 2 H) and 1.82 (s, 6 H). Some starting material was also recovered (55 mg, 45%).

25

EXAMPLE 3**7-Fluoro-9-formyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one****(Compound 24; Structure 12 of Scheme III, where R⁷ = fluoro, R⁹ = formyl,****R⁵⁻⁶ = R⁸ = R¹⁰ = H)**

- 5 MeLi (1.4 M in ether, 0.10 mL, 0.14 mmol) was added to a -70 °C solution of
Compound 20 (50 mg, 0.13 mmol) in THF (12 mL), and the resulting mixture was stirred for
10 minutes before *n*-BuLi (1.6 M in hexane, 0.10 mL, 0.16 mmol) was added. The reaction
mixture was warmed up to -40 °C and then cooled back down to -70 °C. DMF (0.40 mL,
5.0 mmol) was added to the reaction mixture, which was then warmed to room temperature,
10 quenched with water (10 mL) and extracted with EtOAc (2 × 20 mL). Chromatography
afforded 26 mg (61%) of Compound 24 as a white solid. Data for 24: rf = 0.13
(EtOAc:hexanes, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 9.97 (d, *J* = 1.8, 1 H), 9.33 (bs, 1 H),
8.19 (t, *J* = 1.3, 1 H), 7.90 (d, *J* = 8.4, 1 H), 7.61 (dd, *J* = 10.3 and 1.3, 1 H), 7.15 (d, *J* =
8.4, 1 H), 5.51 (s, 2 H) and 1.83 (s, 6 H).

15

EXAMPLE 4**7-Fluoro-9-hydroxyiminomethyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-****2-one (Compound 25; Structure 12 of Scheme III, where R⁷ = fluoro, R⁹ =****hydroxyiminomethyl, R⁵⁻⁶ = R⁸ = R¹⁰ = H)**

- 20 NH₂OH-HCl (10 mg, 0.14 mmol) and pyridine (0.1 mL, 1.4 mmol) were added to a
solution of Compound 24 (20 mg, 0.061 mmol) in ethanol (4 mL), and the resulting mixture
was stirred at room temperature for 1 hour. The reaction mixture was concentrated,
dissolved in EtOAc (30 mL), washed with water and brine, and re-concentrated to afford 18
mg (86%) of Compound 25 as a white solid. Data for 25: rf = 0.11 (EtOAc:hexanes, 1:1);
25 ¹H NMR (400 MHz, acetone-*d*₆) δ 9.27 (s, 1 H), 8.15 (s, 1 H), 7.80 (s, 1 H), 7.78 (d, *J* =
8.3, 1 H), 9.39 (d, *J* = 11.2, 1 H), 7.11 (d, *J* = 8.3, 1 H), 5.39 (s, 2 H) and 1.81 (s, 6 H).

EXAMPLE 5**9-Cyano-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzodioxazin-2-one**

(Compound 26; Structure 12 of Scheme III, where R⁷ = fluoro, R⁹ = cyano, R^{5,6} = R⁸ = R¹⁰ = H)

- 5 Compound 25 (10 mg, 0.029 mmol) was treated with thionyl chloride (0.032 mL, 0.043 mmol) in dichloromethane (10 mL) at room temperature for 40 minutes. The reaction mixture was then quenched with a saturated Na₂CO₃ solution (2 mL), extracted with EtOAc (2 x 20 mL) and washed with brine. Removal of solvent followed by chromatography afforded 8 mg (90%) of Compound 26 as a white solid. Data for 26: rf = 0.32
- 10 (EtOAc:hexanes, 1:1); ¹H NMR (400 MHz, acetone-*d*₆) δ 9.35 (bs, 1 H), 8.05 (t, *J* = 1.5, 1 H), 7.90 (d, *J* = 8.4, 1 H), 7.59 (dd, *J* = 10.6 and 1.5, 1 H), 7.15 (d, *J* = 8.4, 1 H), 5.51 (s, 2 H) and 1.82 (s, 6 H).

Steroid Receptor Activity

- 15 Utilizing the cotransfection assay described by R. M. Evans, *Science*, 240 (1988) 889-895, the disclosure of which is herein incorporated by reference, the compounds of the present invention were tested and found to have strong, specific activity as agonists, partial agonists and antagonists of PR. This assay is described in further detail in the following U.S. Patents, the disclosures of which are incorporated herein by reference: "Retinoic Acid
- 20 Receptor Method", R. M. Evans, E. Ong, P. S. Segui, C. C. Thompson, K. Umesono, V. Giguere, US Patent No. 4,981,784; and "Hormone Receptor-Related Assays", R. M. Evans, C. A. Weinberger, S. M. Hollenberg, V. Giguere, J. Arriza, C. C. Thompson, E. S. Ong, US Patent No. 5,071,773.

- 25 The cotransfection assay provides a method for identifying functional agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native hormones, and for quantifying their activity for responsive intracellular receptor (IR) proteins. In this regard, the cotransfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the cotransfection assay correlates very well with known *in vivo* activity, such that the cotransfection assay functions as a qualitative and quantitative predictor of a tested

compound's *in vivo* pharmacology. See, for example, "Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor", T. S. Berger, Z. Parandoosh, B. W. Perry and R. B. Stein, *J. Steroid Biochem. Molec. Biol.*, 41 (1992) 733-738 (hereinafter "Berger"), the disclosure of which is herein incorporated by reference.

5 In the cotransfection assay, a cloned cDNA for an IR (e.g., human PR, AR or GR) under the control of a constitutive promoter (e.g., the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to make the IR protein of interest. A second gene is also introduced (cotransfected) into the
10 same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), is controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA, then protein) normally expressed by a
15 gene under control of the target receptor and its native hormone.

 The cotransfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, e.g., by increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter
20 transcription. To detect antagonists, the cotransfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (e.g., progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., luciferase production). The cotransfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it
25 determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

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The activities of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and in standard IR binding assays, according to the following illustrative Examples.

5

EXAMPLE 6

Cotransfection assay

The function and detailed preparation procedure of the cotransfection assays have been described previously. See, for example, "Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga *Cymopolia barbata*", C. Pathirana, R. B. Stein, T. S. Berger, W. Fenical, T. Ianiro, D. E. Mais, A. Torres, M. E. Goldman, *Mol. Pharm.*, 47 (1995) 630-635 (hereinafter "Pathirana"). Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts) that had been transiently transfected, using the standard calcium phosphate coprecipitation procedure (see, e.g., Berger), with plasmid containing receptor, MTV-LUC reporter, pRS- β -Gal and filler DNA (Rous sarcoma virus chloramphenical acetyltransferase). The agonist activity was determined by examining the LUC expression (normalized response), and the efficacy readout was a relative value to the maximal LUC expression produced by a reference agonist, e.g., progesterone for hPR, dihydrotestosterone (DHT) for hAR, dexamethasone for hGR, aldosterone for hMR, estradiol for hER. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

20

Receptor Binding Assays

The preparation of receptor binding assays for hPR-A, hGR, and AR has been described (see, e.g., Pathirana).

25

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR, as well as the cross-reactivity of selected compounds on the AR, ER, MR and GR receptors, are shown in Tables 1-2 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and

antagonist compounds indicated above. Also reported in Tables 1-2 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), required to reduce the maximal response by 50%), its agonist potency or EC_{50} (nM).

- 5 Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compound, progesterone (**Prog**), and reference antagonists compound, RU486 and ZK299.

Cmpd	PR Agonist CV-1 Cells		PR Antagonist CV-1 Cells		PR Binding
	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
Prog	100	2.9	na	na	3.5
RU486	na	na	96	0.18	0.58
ZK299	na	na	99	1.6	18
14	30	2500	95	25	172
20	30	500	80	20	17
24	na	na	84	98	181
25	46	623	87	23	65
26	60	1000	68	16	20

na = not active (i.e. efficacy of <20 and potency of >10,000)

nt = not tested

Table 2: Overall agonist and antagonist potency of selected progesterone receptor modulator compounds of present invention and the reference agonist and antagonist compounds shown in Table 1 on PR, AR, ER, GR and MR.

5

Cmpd No.	PR Potency		AR Potency		ER Potency		GR Potency	MR Potency
	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Antag (nM)	Antag (nM)
14	2500	25	na	200	na	na	na	na
20	500	20	na	1000	na	na	na	na
24	na	98	na	130	na	na	na	na
25	623	23	na	100	na	na	na	na
26	1000	16	na	300	na	na	na	na
Prog	3	na	1300	na	na	na	na	nt
RU486	na	0.1	na	12	na	1500	0.7	1100
DHT	na	1800	6	na	1700	na	na	nt
Flut	na	1900	na	26	na	na	na	na
Estr	nt	nt	na	na	7	na	na	nt
ICI 164	na	na	na	na	na	160	na	na
Spir	nt	268	nt	nt	na	na	2000	25

na=not active (i.e., efficacy of >20 and potency of >10,000); nt=not tested

Pharmacological and Other Applications

10

As will be discernible to those skilled in the art, the PR modulator compounds of the present invention can be readily utilized in pharmacological applications where PR antagonist or agonist activity is desired, and where it is desired to minimize cross reactivities with other steroid receptor related IRs. *In vivo* applications of the invention include administration of the disclosed compounds to mammalian subjects, and in particular to humans.

15

The following Example provides illustrative pharmaceutical composition formulations:

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EXAMPLE 7

Hard gelatin capsules are prepared using the following ingredients:

		Quantity (mg/capsule)
5	COMPOUND 26	140
	Starch, dried	100
	Magnesium stearate	<u>10</u>
	Total (mg)	250

10 The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

A tablet is prepared using the ingredients below:

		Quantity (mg/tablet)
15	COMPOUND 26	140
	Cellulose, microcrystalline	200
	Silicon dioxide, fumed	10
	Stearic acid	<u>10</u>
	Total (mg)	360

20 The components are blended and compressed to form tablets each weighing 360 mg.

Tablets, each containing 60 mg of active ingredient, are made as follows:

		Quantity (mg/tablet)
25	COMPOUND 26	60.0
	Starch	45.0
	Cellulose, microcrystalline	35.0
	Polyvinylpyrrolidone (PVP)	
30	(as 10% solution in water)	4.0
	Sodium carboxymethyl starch (SCMS)	4.5
	Magnesium stearate	0.5
	Talc	<u>1.0</u>
	Total (mg)	150.0

35

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The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 °C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, and then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

10	COMPOUND 26	225 mg
	Saturated fatty acid glycerides	<u>2,000 mg</u>
	Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

20	COMPOUND 26	100 mg
	Isotonic saline	1,000 mL
	Glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

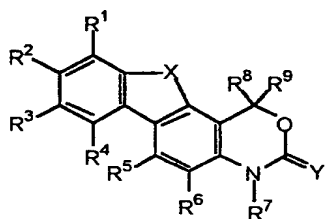
While in accordance with the patent statutes, description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Consequently, for an understanding of the scope of the present invention, reference is made to the following claims.

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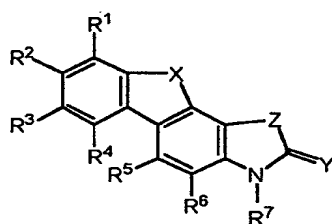
What is claimed is:

1. A compound of the formula:



(I)

OR



(II)

wherein:

R^1 through R^6 are independently hydrogen, F, Cl, Br, I, NO_2 , CN, OR^{10} , $\text{NR}^{10}\text{R}^{11}$, SR^{10} , COR^{12} , CO_2R^{12} , $\text{CONR}^{10}\text{R}^{11}$, optionally substituted C_1 to C_6 alkyl or heteroalkyl, C_1 to C_6 haloalkyl, optionally substituted C_3 to C_8 cycloalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted aryl or heteroaryl, or optionally substituted arylmethyl, where R^{10} and R^{11} are independently hydrogen, C_1 to C_6 alkyl or heteroalkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl, optionally substituted arylmethyl, COR^{13} , SO_2R^{13} or S(O)R^{13} , where R^{12} is hydrogen, C_1 to C_6 alkyl or heteroalkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl or optionally substituted

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arylmethyl, where R^{13} is hydrogen, C_1 to C_6 alkyl or haloalkyl, aryl, heteroaryl, optionally substituted allyl or optionally substituted arylmethyl;

R^7 is hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, aryl, arylmethyl, heteroaryl, COR^{12} , CO_2R^{12} , SO_2R^{12} , $S(O)R^{12}$ or $CONR^{10}R^{11}$, where R^{10-12} have the same definitions given above;

R^8 and R^9 are independently hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted arylmethyl, optionally substituted aryl or optionally substituted heteroaryl;

X is OCH_2 , SCH_2 , $NHCH_2$, $OC(O)$, $SC(O)$, $NHC(O)$, CH_2O , CH_2S , CH_2NH , $C(O)O$, $C(O)S$ or $C(O)NH$;

Y is O, S or NR^{10} , where R^{10} has the same definition given above; and

Z is O, S, NR^{14} , $CR^{14}R^{15}$, $CR^{14}R^{15}CR^{16}R^{17}$, $OCR^{14}R^{15}$, $SCR^{14}R^{15}$, $CR^{14}R^{15}S$, $NR^{14}CR^{15}R^{16}$, or $CR^{14}R^{15}NR^{16}$, where R^{14} through R^{17} each independently are hydrogen, C_1 to C_6 alkyl or haloalkyl or heteroalkyl, optionally substituted C_2 to C_6 alkenyl or alkynyl, optionally substituted allyl, optionally substituted arylmethyl, optionally substituted aryl or optionally substituted heteroaryl;
or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of: 7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 14); 9-bromo-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 20); 7-fluoro-9-formyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 24); 7-fluoro-9-hydroxyiminomethyl-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 25); 9-cyano-7-fluoro-4,4-dimethyl-5H-chromeno[3,4-f]-1,3-benzo[d]oxazin-2-one (Compound 26).

3. A pharmaceutical composition comprising, in a pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compounds as claimed in Claim 1.

4. A compound of Claim 1 wherein said compound modulates a process mediated by one or more steroid receptors from the group consisting of progesterone receptors and androgen receptors.

5. A compound of Claim 1, wherein said compound modulates female hormone responsive diseases.

6. A compound of Claim 1 wherein said compound modulates male hormone responsive diseases.

7. A method of using a compound of Claim 1 to treat a hormone responsive disease wherein the compound is administered in combination with a progesterone receptor agonist, an estrogen receptor agonist, or both.

8. A method of inducing contraception in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

9. A method of treatment or prevention in a mammal of carcinomas or adenocarcinomas of the endometrium, ovary, breast, colon or prostate, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

10. A method of treating or preventing benign or malignant neoplastic disease in a mammal, the method comprising administering to a mammal in need thereof a

pharmaceutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

11. The method of Claim 10 wherein the benign or malignant neoplastic disease is selected from uterine fibroids, endometriosis, benign prostatic hypertrophy, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate or pituitary, meningioma, or other hormone-dependent tumors.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 November 2000 (09.11.2000)

PCT

(10) International Publication Number
WO 00/66590 A3

(51) International Patent Classification⁷: C07D 498/04,
A61K 31/5383, A61P 35/00, 5/32 // (C07D 498/04,
311:00, 265:00)

(21) International Application Number: PCT/US00/11750

(22) International Filing Date: 1 May 2000 (01.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/304,614 4 May 1999 (04.05.1999) US
09/552,353 19 April 2000 (19.04.2000) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 09/552,353 (CON)
Filed on 19 April 2000 (19.04.2000)

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

(88) Date of publication of the international search report:
8 February 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 00/66590 A3

(54) Title: TETRACYCLIC PROGESTERONE RECEPTOR MODULATOR COMPOUNDS AND METHODS

(57) Abstract: Nonsteroidal compounds that are high affinity, high selectivity modulators for progesterone receptors are disclosed. Also disclosed are pharmaceutical compositions incorporating such compounds, methods for employing the disclosed compounds and compositions for treating patients requiring progesterone receptor agonist, partial agonist or antagonist therapy, intermediates useful in the preparation of the compounds and processes for the preparation of the progesterone receptor modulator compounds.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/11750

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D498/04 A61K31/5383 A61P35/00 A61P5/32 //(C07D498/04,311:00,265:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 19458 A (LIGAND PHARM INC) 27 June 1996 (1996-06-27) cited in the application abstract; claims	1,7-11
A	US 5 688 808 A (HAMANN LAWRENCE G ET AL) 18 November 1997 (1997-11-18) cited in the application abstract; claims	1,7-11
A	US 5 693 646 A (ZHI LIN ET AL) 2 December 1997 (1997-12-02) cited in the application abstract; claims	1,7-11
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
24 November 2000		06/12/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer
		Paisdor, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/11750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 693 647 A (HAMANN LAWRENCE G ET AL) 2 December 1997 (1997-12-02) cited in the application abstract; claims</p> <p>-----</p>	1,7-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/11750

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619458 A	27-06-1996	US 5688810 A	18-11-1997
		US 5688808 A	18-11-1997
		US 5693647 A	02-12-1997
		US 5696127 A	09-12-1997
		US 5693646 A	02-12-1997
		US 5696130 A	09-12-1997
		US 5696133 A	09-12-1997
		AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A	16-09-1998
		EP 1043325 A	11-10-2000
		EP 1043326 A	11-10-2000
		EP 1041071 A	04-10-2000
		EP 1041066 A	04-10-2000
		EP 1043315 A	11-10-2000
		EP 0800519 A	15-10-1997
		HU 78117 A	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		US 6093821 A	25-07-2000
		US 5994544 A	30-11-1999
		US 6121450 A	19-09-2000
US 5688808 A	18-11-1997	AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A	16-09-1998
		EP 1043325 A	11-10-2000
		EP 1043326 A	11-10-2000
		EP 1041071 A	04-10-2000
		EP 1041066 A	04-10-2000
		EP 1043315 A	11-10-2000
		EP 0800519 A	15-10-1997
		HU 78117 A	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		WO 9619458 A	27-06-1996
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		US 5696130 A	09-12-1997
		US 5693646 A	02-12-1997
		US 5688810 A	18-11-1997
		US 5693647 A	02-12-1997
		US 5696127 A	09-12-1997
		US 5696133 A	09-12-1997
		US 6093821 A	25-07-2000
		US 5994544 A	30-11-1999
		US 6121450 A	19-09-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/11750

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5693646 A	02-12-1997	AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A	16-09-1998
		EP 1043325 A	11-10-2000
		EP 1043326 A	11-10-2000
		EP 1041071 A	04-10-2000
		EP 1041066 A	04-10-2000
		EP 1043315 A	11-10-2000
		EP 0800519 A	15-10-1997
		HU 78117 A	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		WO 9619458 A	27-06-1996
		US 5994544 A	30-11-1999
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		US 5696130 A	09-12-1997
		US 5688808 A	18-11-1997
		US 5688810 A	18-11-1997
		US 5693647 A	02-12-1997
		US 5696127 A	09-12-1997
		US 5696133 A	09-12-1997
		US 6093821 A	25-07-2000
		US 6121450 A	19-09-2000
US 5693647 A	02-12-1997	AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A	16-09-1998
		EP 1043325 A	11-10-2000
		EP 1043326 A	11-10-2000
		EP 1041071 A	04-10-2000
		EP 1041066 A	04-10-2000
		EP 1043315 A	11-10-2000
		EP 0800519 A	15-10-1997
		HU 78117 A	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		WO 9619458 A	27-06-1996
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		US 5696130 A	09-12-1997
		US 5688808 A	18-11-1997
		US 5693646 A	02-12-1997
		US 5688810 A	18-11-1997
		US 5696127 A	09-12-1997
		US 5696133 A	09-12-1997
		US 6093821 A	25-07-2000
		US 5994544 A	30-11-1999
		US 6121450 A	19-09-2000